Docket No.: 2815-0347PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brian FROSTRUP et al.

Application No.: 10/566,384 | Confirmation No.: 5532

Filed: January 30, 2006 | Art Unit: 4161

For: 2-METHOXYMETHYL-3-(3,4-DICHLOROPHENYL)-8-AZABICYCLO[3.2.1]OCTANE TARTRATE SALTS | Examiner: Valerie Rodriguez-Garcia

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Brian Frøstrup, declare the following:

I am the Head of Preformulation at NeuroSearch of Ballerup, Denmark.

A copy of my curriculum vitae is attached hereto.

I have read and understand the specification and claims to the above-identified application and the outstanding Office Action of July 10, 2008 (hereinafter "Office Action").

I have also read and considered within the Office Action the 35 U.S.C. 103(a) rejection.

As to the above rejection, the Examiner cites Scheel-Kruger *et al.*, US Patent No. 6,288,079 B1 (which is the U.S. equivalent to WO 97/30997) in which the citrate salt is mentioned.

Below is data that shows that the salt of the present invention, when compared to the citrate salt of Scheel-Kruger *et al.*, shows an unexpected substantial improvement in hygroscopic properties. The non-hygroscopic nature of the tartrate salt is important for any commercial use. Scheel-Kruger *et al.* do not teach or suggest that the tartrate salt would possess any such special properties. Based on the above, as well as the data below, the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

The above arguments and the data explained below were presented to the International Preliminary Examining Authority (IPEA) when replying to the First Written Opinion of the ISA. Based on the above submission, the IPEA acknowledged the inventive step of the claimed invention. Enclosed is Exhibit A, which is a copy of the positive International Preliminary Report on Patentability (IPRP), for the Examiner' convenience and consideration. The IPRP discussed the data presented below.

In support of the Response to the Office Action, the following data is presented:

Hygroscopicity as measured by Dynamic Vapour Sorption (DVS)

The citrate salt and the L-tartrate salt (monohydrate) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane were tested for their water sorption characteristics as a function of increasing and decreasing humidity.

The sample weight was taken as the dry weight after equilibration at 0%RH (relative humidity). The adsorption cycles were sequentially stepped at 10% intervals from 0% to 95%RH.

The desorption cycle was the reverse of the adsorption cycle and was sequential after the adsorption cycle. A second adsorption-desorption cycle was also sequentially performed.

Citrate salt

The DSV sorption profile for the citrate salt is shown in Figure 1. The profile shows the salt to be hygroscopic. The mass increase of up to 3% at ambient relative humidity indicates the formation of a monohydrate. At high relative humidity the mass increase is 15% or more. When decreasing the relative humidity, the salt keeps about 5 % mass increase.

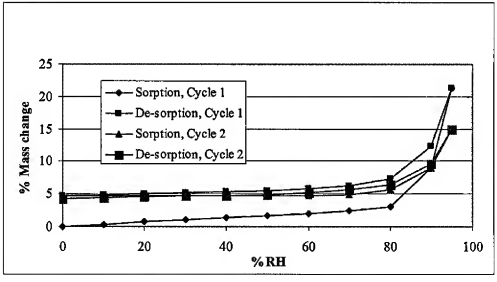

Figure 1. DSV sorption profile of the citrate salt.

Tartrate salt

The DSV sorption profile for the tartrate salt is shown in Figure 2. The profile shows the salt to be non-hygroscopic. A mass increase (up to 0.16 %) was due to adsorption on the surface of the compound.

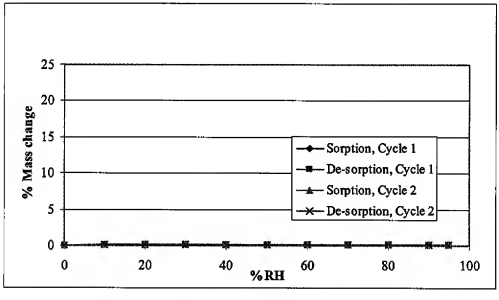

Figure 2. DSV sorption profile of the tartrate salt.

Thus, based on the above data, when compared to the citrate salt of Scheel-Kruger *et al.*, the salt of the present invention shows an unexpected substantial improvement in hygroscopic properties. As indicated in the data, the DSV sorption profile for the citrate salt (as shown in Figure 1) shows the citrate salt to be hygroscopic. The mass increase at ambient relative humidity indicates the formation of a monohydrate. When comparing the present invention to the citrate salt, for cycle 1, there is a near 20% improvement in mass change at high relative humidity. At decreasing humidity there is still a baseline improvement of 5% change in mass.

Also indicated is a near 15% improvement in mass change for cycle 2 at high relative humidity and the same baseline improvement of 5% change in mass.

As indicated, the non-hygroscopic nature of the tartrate salt is important for any commercial use. Scheel-Kruger *et al.* do not teach or suggest that the tartrate salt would possess any such special properties. The data provided shows that the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

STATEMENT UNDER 18 U.S.C. § 1001

I hereby declare that all statements made herein of any own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: _____

_____
Brian Frøstrup

Enclosures: Exhibit A: International Preliminary Report on Patentability

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

NEUROSEARCH A/S
Patent Department
93 Pederstrupvej
DK-2750 Ballerup
DANEMARK

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	23.05.2005

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
264-204-WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/051651	29.07.2004	31.07.2003

Applicant
NEUROSEARCH A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Parriche, S Tel. +49 89 2399-7890

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 264-204-WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/051651	International filing date *(day/month/year)* 29.07.2004	Priority date *(day/month/year)* 31.07.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/46, A61P25/00, C07D451/02

Applicant
NEUROSEARCH A/S et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.03.2005	23.05.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Molina de Alba, J Telephone No. +49 89 2399-7823

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-12 as originally filed

   Claims, Numbers

   1-12 received on 19.03.2005 with letter of 19.03.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	12?

2. Citations and explanations (Rule 70.7):

see separate sheet

1) Reference is made to the following document:

D1: WO 97/30997 A (NEUROSEARCH AS ; SCHEEL KRUEGER JOERGEN (DK); MOLDT PETER (DK); WAETJE) 28 August 1997 (1997-08-28)

2) The present application relates to (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts and their use as monoamine neurotransmitter re-uptake inhibitors.

3) Re Item V

3.1 Novelty (Art. 33(2) PCT)

None of the cited documents discloses the particular compound (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate. The claimed subject-matter is therefore regarded as novel.

3.2 Inventive Step (Art. 33(3) PCT)

D1 is considered to be the closest state of the art. This document relates (cf. abstract and pg. 1, par. 1) to the preparation of particular tropane derivatives and their use as monoamine neurotransmitter re-uptake inhibitors in the treatment of disorders such as Parkinson's disease, depression, obsessive compulsive disorders, panic disorders, dementia, etc. For the preparation of the medicinal compositions, **D1** suggests (cf. pg. 7, par. 1) as pharmaceutically acceptable salts a list of acid addition salts comprising **tartrate**. It is also mentioned (cf. pg. 8, par. 6), that the resolution of racemic mixtures may be carried out by fractional crystallization of D- or **L-tartrates**, mandelates, or camphorsulphonates. Example 15 of **D1** discloses the preparation of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane and its **citrate** salt.

The subject-matter of the application differs from **D1** in that the compound involved is a **tartrate** and not to a citrate. The Applicant has shown by means of comparative examples (filed on 19.03.2005) that the tartrate of the invention shows much better properties as regards hygroscopicity than its homologous citrate salt. The problem to be solved by the present

application may thus be regarded as providing **less hygroscopic** salts of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane.

Even though **D1** mentions (see paragraphs indicated above) tartrates among the suitable pharmaceutical salts, this document is silent as to the hygroscopic properties of the resulting substances. Thus, there is no motivation in **D1** for the skilled person to particularly select tartrates among other pharmaceutically acceptable salts. As this selection is accompanied by an unexpected effect (drastically low hygroscopic character) the claimed subject-matter involves an inventive step.

3.3 Industrial applicability (Art. 33(4) PCT)

Is acknowledged for claims 1-11.

For the assessment of the present Claim 12 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States and the patentability can also be dependent upon the formulation of the claims.